clear view. If traction is maintained on the spleen, pancreas, and splenic vessels the tension on the splenic artery is transmitted to the coeliac axis and consequently to the aorta and renal artery, and the adrenal vessels and sympathetic nerves, and so the adrenal gland itself, are fixed. This manœuvre may alter the position of the gland, to the operator's advantage, by 3–4 cm. (Fig. 2). The gland can then be dissected under vision, its vessels ligated, and the gland removed entire. The retroperitoneum in the area is then inspected for the presence of accessory adrenal tissue.

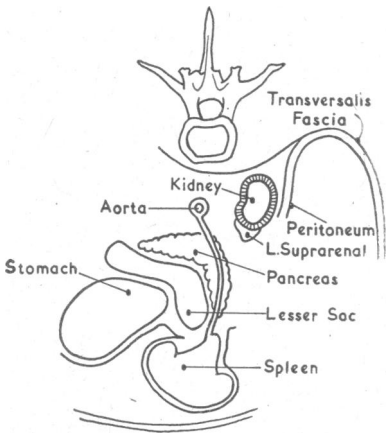

FIG. 2.—Spleen mobilized with splenic vessels and pancreas to expose left suprarenal gland.

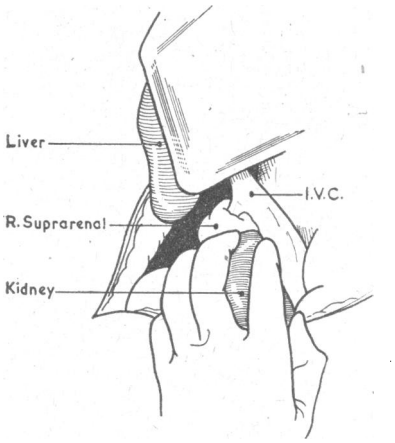

FIG. 3.—Kidney manually retracted downwards, liver upwards, inferior vena cava to patient's left. Right suprarenal gland exposed.

Attention is now turned to the right side, and the right adrenal is sought in the area bounded by the lower border of the right lobe of the liver, the right edge of the vena cava, the upper border of the renal vessels, and the upper pole of the right kidney. If the liver is bulky or situated in a particularly low position, it is helpful to divide between forceps the falciform ligament and the right triangular ligament. A retractor is gently inserted to draw the liver upwards. This retraction must be carefully done, for the liver in this particular situation is easily torn. The upper pole of the kidney is then depressed by two fingers; one, placed medially in relation to the upper pole, pressing downwards on the renal artery, and the other on the outer edge of the upper pole. When this has been done, an area of peritoneum a few centimetres in diameter is excised from the hepato-renal pouch. Incision of this peritoneum is not sufficient: the edges of such an incision do not always separate well. When this patch of peritoneum has been removed the adrenal gland comes under vision. Vision is improved by rolling the patient over a little towards her left side.

A retractor can now be inserted to roll away gently the right edge of the vena cava. The outer border of the gland is first dissected free, and then the inner border is freed by careful division between ligatures of the fascia which binds the adrenal to the sheath of the vena cava. The main vein can be seen clearly passing over the front of the medial part of the gland to reach the vena cava (Fig. 3). This vein is not so well seen when the operation is done from behind. When this vein is ligated, the gland can be easily separated from the vena cava and the separation is continued upwards. A long tongue of tissue usually extends upwards behind the right edge of the vena cava, but after division of the main vein, and retraction of the right edge of the vena cava, it is usually possible to surround it gradually by successive pairs of forceps. Only after the medial and lateral borders of the gland, and the upper pole, have been freed, is dissection of the lower surface of the gland completed, between adrenal and kidney. The attachment of the adrenal to the perirenal fascia here maintains that convenient low position of the adrenal which has usually been obtained initially by depression of the kidney. The only danger of the operation on this side is the risk of venous haemorrhage when the dissection is being carried round the extreme upper pole. An ordinary sponge-holding forceps makes a suitably gentle holder for the adrenal gland during dissection.

MALE PSEUDOHERMAPHRODITISM: A HITHERTO UNDESCRIBED FORM

BY

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Of recent years considerable progress has been made in the clinical differentiation of intersexuality, and a now well-recognized form of male pseudohermaphroditism has emerged. Schneider *et al.* (1952) laid down the following criteria for the diagnosis of this type, referred to as "intersex males with purely feminine external genitalia and bodily habitus" by Williams (1952): feminine habitus, primary amenorrhoea, absence or almost complete absence of axillary and pubic hair, blind vaginal pouch with absent cervix, and intra-abdominal testes. They could find only 12 cases in the literature which fulfilled their criteria, and reported six cases of their own. Two further cases have been reported by Beatty *et al.* (1953) and by Armstrong (1953, 1955).

With the introduction of relatively simple techniques for the determination of chromosomal—that is, genetic—sex, first by the skin biopsy method (Moore *et al.*, 1953) and more recently by the even simpler polymorphonuclear leucocyte method (Davidson and Robertson Smith, 1954), a new and potent tool has become available for the elucidation of problems of intersexuality. Already it has been demonstrated that many examples of so-called Turner's syndrome (ovarian—or, better, gonadal—agenesis) are of male chromosomal sex though outwardly of female appearance (Polani *et al.*, 1954; Wilkins *et al.*, 1954; Russell *et al.*, 1955). The application of these techniques to two patients presenting with primary amenorrhoea led to their diagnosis as male pseudohermaphrodites, of a type apparently undescribed in the literature, and which forms the subject of the following report.

Case 1

This patient, aged 19, was referred on account of primary amenorrhoea. The mother and father are normal, and there is a normal sister, aged 16½, whose menarche occurred at about 15 and whose menstruation has remained regular. The patient is about 6 in. (15 cm.) taller than her sister, a little taller than her mother, and the same height as her father. She was of normal height until 11 or 12, when she began to grow rapidly, and is now one of the tallest in the family, which includes no other known examples of sexual abnormality. She has always been thin. The past history included chicken-pox and measles in childhood but no other significant illnesses. The social history was quite uneventful. The patient works as a typist and is happy in her occupation.

Her interests are entirely feminine and appropriate to her age, though socially she is rather retiring, has no boy friends, and does not dance.

On physical examination (Fig. 1) her height was found to be 69 in. (175 cm.), span 71 in. (180 cm.), lower measurement 36 in. (91 cm.), and upper measurement 33 in. (84 cm.); these are definitely eunuchoid proportions. Her weight was 116 lb. (52.6 kg.) and her leanness was quite noticeable. Her voice was that of a girl. The breasts were undeveloped, the nipples and areolae small. The scalp hair was normal and there was a little hair on the upper lip. Hair was present in moderate amount in the axillae and more extensively on the pubis. There was also some hair on the arms and legs. The skin and musculature were normal. The pulse was 80 a minute and the blood pressure 130/80. There was nothing remarkable in the chest or abdomen and there were no inguinal herniae. The external genitalia were of female type, apparently normal except for marked enlargement of the clitoris (Fig. 2), and the labia minora were prominent. A vaginal smear was markedly hypo-oestrogenic.

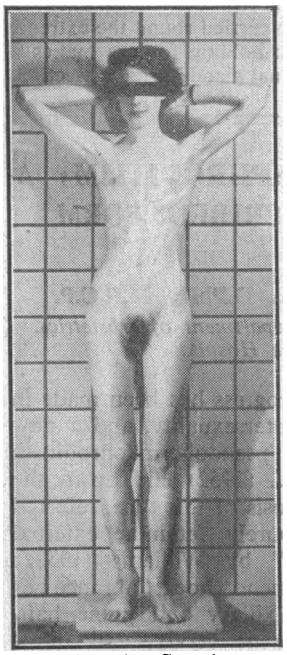

FIG. 1.—Case 1.

The physical findings suggested adrenal hyperplasia producing female pseudohermaphroditism, and she was admitted to hospital for further investigation. Examination under anaesthesia showed the clitoris to measure 4.5 by 1.25 cm. The hymen was small and intact, the vagina about normal in size but with poorly developed rugae. A normal cervix was present, but the uterus was extremely small — about 1 in. (2.5 cm.) long. No adnexa could be felt. A skin biopsy was taken from the medial aspects of the thigh.

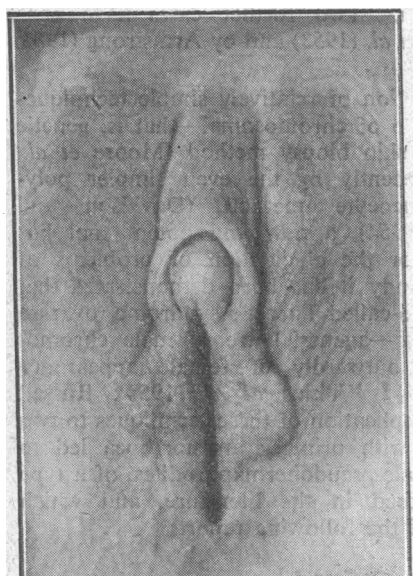

FIG. 2.—Showing enlargement of the clitoris in Case 1.

Laboratory Investigations.—Haemoglobin, 95%; leucocytes, 6,100 per c.mm. (neutrophils 56.5%, lymphocytes 37%, monocytes 5%, eosinophils 1.5%, basophils 0%). Plasma sodium, 146.5 mEq/l.; potassium, 4.7 mEq/l. Urinary neutral 17-ketosteroids, 6.6 mg./24 hours. Urinary oestrogens: oestrone 5.3, oestradiol nil, oestriol 40 μg./24 hours. Urinary gonadotrophins (kaolin adsorption and mouse uterine weight method): nearly 20 mouse units/24 hours. Blood film for genetic sex, male (confirmed by Dr. W. M. Davidson).

Since January, 1955, the patient has had two courses of stilboestrol, each of 20 days. At first the daily dose was 1 mg. and subsequently it was 2 mg. An interval of ten days was allowed to elapse between each 20-day course of tablets. So far (May, 1955) there have been no oestrogen withdrawal bleedings, but a little mammary enlargement has occurred.

Case 2

This patient, aged 24, was also referred on account of primary amenorrhoea. When aged 17 she was seen by a gynaecologist, who stated that the ovaries had not developed and that she would never menstruate. She has four sisters, all older than herself, and all with normal menstruation; three are married with children. There are also a married brother with children, and an unmarried brother. She had measles, mumps, and a tonsillectomy in childhood; apart from these, her past medical history is unimportant. She has a normal feminine outlook and libido, and she works as a machine operator.

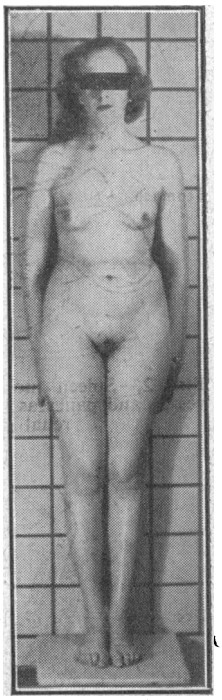

FIG. 3.—Case 2. After three months of oestrogen therapy. The pubic hair had been shaved for the previous examination under anaesthesia and some regrowth had occurred.

Her general appearance was that of a tall, eunuchoidal female. Her height was 70½ in. (179 cm.), span 75 in. (190 cm.), upper measurement 34 in. (86 cm.), lower measurement 36½ in. (93 cm.), weight 149 lb. (67.6 kg.). Her voice was noticeably deep. Her breasts were poorly developed, containing a small amount of mammary tissue. The skin was normal, except for the presence of a few pigmented moles and a spider telangiectasis on the neck. The scalp hair was normal; axillary and pubic hair was present, though rather scanty. The musculature was normal, as were the pulse (76 a minute) and blood pressure (120/70). There was nothing remarkable in the chest or abdomen, and there were no inguinal herniae. The external genitalia were of female type and apparently normal, with no enlargement of the clitoris. The vagina was of normal length, but a vaginal smear was markedly hypo-oestrogenic.

She was admitted to hospital for investigation. Examination under anaesthesia confirmed the normality of the vulva, clitoris, and vagina, except for the poor rugose development of the latter. The cervix was small, but not minute; the uterus was rudimentary, not exceeding 1 in. (2.5 cm.) in length. No adnexa could be felt. A skin biopsy was taken from the medial aspect of the thigh.

Laboratory Investigations.—Haemoglobin, 96%; leucocytes, 6,600 per c.mm. (neutrophils 46%, lymphocytes 40%, monocytes 11.5%, eosinophils 2%, basophils 0.5%). Plasma cholesterol, 153 mg. per 100 ml. B.M.R., −5.5 and −6.5%. Urinary neutral 17-ketosteroids, 8.3 mg./24 hours. Urinary oestrogens: oestrone 4.2, oestradiol 2.8, oestriol 17 μg./24 hours. Urinary gonadotrophins, less than 5 mouse units /24 hours. Blood film for genetic sex, male (confirmed by Dr. W. M. Davidson). *X*-ray films of the pelvis revealed a masculine configuration, and the radiological bone age was estimated as 18–20 years—that is, 4 to 6 years retarded.

Since February, 1955, she has been taking ethinyloestradiol, 0.1 mg. daily, in 20-day courses, with 10 days between each course. A scanty oestrogen withdrawal bleeding followed the second course, and some enlargement of the breasts has occurred. Fig. 3 shows the patient after three months of treatment.

Discussion

First, it is pertinent to point out that it has been found easier to reach a decision regarding the chromosomal sex from a study of leucocytes in blood films than from skin biopsies, though the findings in the latter have been consistent with the conclusions reached from blood-film studies. Because these conclusions were so surprising, blood films were sent to Dr. W. M. Davidson, who very kindly reported on them, *without having been informed of the clinical features of the patients.* His interpretation, which confirmed my own, was thus completely unbiased, and, since there have so far been no reports of erroneous results from the method of chromosomal sex determination, it seems justifiable to regard these two patients as of male genetic sex.

The possibility that Case 1 was an example of adrenal hyperplasia causing female pseudohermaphroditism was ruled out by the finding of a normal 17-ketosteroid excretion, and the true state of affairs was revealed by the blood film.

The patients had the following features in common: they presented as "females" complaining of primary amenorrhoea; they were tall, with eunuchoidal proportions; there was little or no mammary development, and pubic and axillary hair was present in essentially normal amounts; the vagina was of normal length, though with evidence from the mucosa of marked oestrogen deficiency; the cervix was almost normal but the uterus was very small; no adnexa could be palpated; the 17-ketosteroids were in the normal range and the urinary oestrogens definitely higher than usually found in primary amenorrhoea; the chromosomal sex was male. The only important differences between the patients were the presence of a definitely enlarged clitoris in one, who also had a significant (normal) output of urinary gonadotrophins, and of a rather deep voice in the other. It would, of course, have been of great interest to determine the histological status of the gonads, but it was felt that laparotomy could not be justified solely on the grounds of scientific curiosity.

The differentiation of this type of male pseudohermaphroditism from the more generally recognized form of "intersex males with purely feminine external genitalia and bodily habitus" depends upon the presence of body hair and normal vagina and cervix in the former and their deficiency in the latter, together with the deficiency of mammary development in the former and its relative normality in the latter. It is also of interest that whereas in the two cases described here the oestrogen excretion was not unlike that found in normal females, while the vaginal smears appeared to be very hypo-oestrogenic, in the male pseudohermaphrodites reported by Beatty *et al.* (1953) and by Armstrong (1955) the oestrogens were oestrone 1.5, oestradiol 2.5, oestriol 2.0 μg./24 hours for the former (whose vaginal smear showed definite evidence of oestrogenic stimulation) and oestrone 2.44 and 3.1, oestradiol 0.5 and 1.4, and oestriol 2.0 and 1.6 μg./24 hours for the latter. It is tempting to postulate an enhanced tissue responsiveness to oestrogens in the "classical" male pseudohermaphrodite and a decreased responsiveness in the patients reported here, though it must be admitted that one, at any rate, has shown sufficient endometrial responsiveness to have oestrogen withdrawal bleedings.

The other conditions from which this new type of male pseudohermaphroditism should be differentiated are the gonadal agenesis syndrome ("Turner's syndrome") and primary and secondary female hypogonadism. In the gonadal agenesis syndrome the patient is short and stocky, often showing various congenital anomalies such as webbed neck, cubitus valgus, coarctation of the aorta, squints, polydactyly, and so forth; there is no mammary development, and body hair is scanty or absent; the vagina and uterus are infantile; the urinary gonadotrophins are usually high and the oestrogen excretion is low; and the chromosomal sex may be male or female. In primary (excluding the above) and secondary hypogonadism the chromosomal sex is female; mammary development is absent and the genitalia are infantile; the height may be increased in primary, and normal, increased, or decreased in secondary hypogonadism; body hair is scanty or absent; the urinary gonadotrophins are increased in primary and decreased in secondary hypogonadism, while the oestrogen excretion is low in both. These differential features are summarized in the Table.

Thus, apart from the clinical features, these various causes of primary amenorrhoea require for their differentiation chromosomal sex determination (by leucocyte or skin biopsy techniques) and urinary gonadotrophin estimation. Determination of the oestrogen excretion is helpful but not necessary; examination of the vaginal smear is also helpful, and is much easier to carry out.

With the new type of male pseudohermaphroditism reported in this paper, it would seem that there are at least three forms of "intersex male with purely feminine external genitalia and bodily habitus"—that is, in addition to this new type, the "classical" type and the gonadal agenesis syndrome. A logical interpretation of the intersexualizing process is available for the last type: the experimental work of Jost (1947) and of Raynaud and Frilley (1947) has shown that removal or the destruction of the gonads of embryos in mice and rabbits in the sexually indeterminate stage leads to the development of foetuses all of which are apparently female, the males having undergone intersexualization; it seems probable that a failure of migration of the primordial germ cells, the sex of which is already determined genetically, from the yolk sac endoderm to the cortex of the genital ridge would result in failure of differentiation of the cortical elements of the gonad (which evidently have an endocrine influence in the normal male embryo) and so lead to the same intersexualization as that demonstrated experimentally by Jost and by Raynaud and Frilley.

This interpretation cannot apply to the "classical" type of male pseudohermaphrodite, in which the gonads appear to be intact and are indistinguishable from undescended testicles found in otherwise normal males. The evidence suggests that the abnormality in these patients consists in an increased tissue sensitivity to oestrogens; the existence of such a state in the sexually undifferentiated embryo would then lead to

Differential Diagnosis of Primary Amenorrhoea (excluding imperforate hymen, uterine agenesis, and other purely anatomical causes)

	Stature	Congenital Anomalies	Breasts	Body Hair	Vagina	Cervix	Chromosomal Sex	Gonadotrophins	Oestrogens
"Classical" male pseudohermaphroditism	Normal or tall	—	Developed	Absent or very scanty	Short, oestrogenized at least in some	Minute or absent	Male	Normal	Low
New type of mal pseudohermaphroditism	,, ,, ,,	—	Little or no development	Within normal limits	Normal, unoestrogenized	Normal	,,	,,	Apparently normal
Gonadal agenesis syndrome	Short	Frequent	Undeveloped	Absent or scanty	Infantile	Infantile	Male or female	High	Low
Primary female hypogonadism	Tall	—	,,	,, ,,	,,	,,	Female	,,	,,
Secondary female hypogonadism	Tall, normal, or short	—	,,	,, ,,	,,	,,	,,	Low	,,

the same form of intersexualization as described above. Since a familial tendency to this type of male pseudohermaphroditism has been reported (Schneider *et al.*, 1952) one may suppose that the postulated oestrogen hypersensitivity is genetically determined. This explanation will not suffice for the new type, where the oestrogen levels seem to be higher and yet there is little or no mammary development and the vaginal smear appears to be hypo-oestrogenic. In the absence of factual knowledge of the gonadal structure in these patients it is probably better to refrain from speculation on the mechanism of intersexualization.

Summary

Two examples of a new and apparently undescribed type of male pseudohermaphroditism are reported. Both patients presented as eunuchoidal "females" complaining of primary amenorrhoea. They had normal axillary and pubic hair, little or no mammary development, and normal external genitalia, except for marked enlargement of the clitoris in one. The cervix was about normal, but the uterus was rudimentary and the vaginal smear was markedly hypo-oestrogenic. The urinary 17-ketosteroids were normal, and the oestrogen levels seemed to be definitely higher than those found in other cases of primary amenorrhoea. The gonadotrophins were low in one and normal in the other. The chromosomal sex, as determined by blood-film studies, and confirmed by skin biopsies, was male.

The differentiation of this type of male pseudohermaphroditism from the generally recognized variety of "intersex male with purely feminine external genitalia and bodily habitus" and from other relevant forms of hypogonadism is discussed.

I am indebted to Dr. W. M. Davidson for examining and reporting on the blood films, and to Dr. Sylvia Dawkins, who referred Case 1, and Dr. E. E. Pochin, who referred Case 2, for permission to include these cases in the report.

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ADDENDUM.—Since this paper was written R. B. Greenblatt and N. Carmona (*J. clin. Endocr.*, 1955, **15**, 877) have described the case of a 25-year-old tall "female" of eunuchoidal appearance with primary amenorrhoea, failure of breast development, infantile uterus, scanty pubic hair, and markedly enlarged clitoris. The chromosomal sex was male, the vaginal smear was atrophic, the urinary 17-ketosteroids were decreased, and the gonadotrophins were within normal limits. This case resembles very closely Case 1 described above. Laparotomy revealed rudimentary gonads, histological examination of which showed a cortex composed of stroma without follicles and a medulla and hilus containing many "Leydig cells."

The Haemophilia Society, whose president is Sir LIONEL WHITBY, has produced a pamphlet describing its purposes. *The Haemophilia Society: What it is and How it can Help* may be obtained from the hon. secretary, 94, Southwark Bridge Road, London, S.E.1. The society's aims include the provision of fellowship, advice, and help for the individual haemophilic and promotion of the study of the disease. Membership is open to all haemophilics, their families, and friends. The minimum subscription is 5s. a year.

EUNUCHOIDISM IN IDENTICAL TWINS
WITH CONGENITAL FUSION OF THE THORACIC VERTEBRAE

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The occurrence of congenital developmental abnormalities in twins, uniovular or binovular, is not unusual, and numerous instances have been reported in the literature. The abnormality may be single, or multiple abnormalities may coexist, and any of the systems may be involved. Endocrine disturbances may occur, and infantilism and pituitary dwarfism in identical male twins have been reported by van Braam Houckgeest and Sanders (1940) and Guillain and Rouzaud (1943), in the latter instance accompanied by retardation of intellectual development and the presence of major epilepsy in one of the twins. A careful search of the literature, however, has not disclosed any report of eunuchoidism in identical twins, and the following is therefore of interest.

Case 1

A dustman aged 40 complained of having had painless swelling of the feet and ankles for a fortnight. There was obvious endocrine disturbance, and he was admitted to hospital for further investigation.

He was one of twin brothers. He had always been of large physique, and the brothers were the biggest pupils in their class at school, but were poor scholars and did not reach a high standard before leaving school at the age of 14. He had never shaved. He was unmarried, and had shown no interest in the female sex, but admitted to masturbating about twice monthly with ejaculation, although spontaneous nocturnal emissions had not occurred. He said he drank 12 pints (6.8 litres) of fluid a day and passed large quantities of urine. Tibial osteotomy for genu valgum had been performed when he was aged 16.

On examination he was found to be mentally backward, of placid temperament, very lethargic, unruffled, and easy to please, and was indifferent to his physical condition apart from the recent ankle oedema. He looked younger than his years, and the voice was high-pitched and unbroken. The skin of the face was smooth and devoid of hair, and the axillary and pubic hair was sparse, the latter being of female distribution. There was considerable obesity, the fat being of "buffalo" distribution, with gynaecomastia and colourless striae of the abdomen. The limbs were excessively long and genu valgum was present, but his height was diminished by a gross dorsal kyphosis. The genitalia were of infantile proportions, and the testes, the size of small beans, were fully descended into the scrotum (Fig. 1). The prostate could not be felt on rectal examination.

Examination of the systems revealed no gross abnormality. The heart sounds were normal and the blood pressure was 160/100. There was no optic atrophy and the visual fields were full. Pitting oedema was present over the lower third of both legs.

The following investigations were carried out: haemoglobin, 92% (13.6 g.%); Wassermann reaction negative; blood urea, 24 mg. per 100 ml. Urinalysis: albumin present; pus cells present in moderate numbers; red cells present in large numbers; casts absent; moderate numbers of calcium oxalate crystals seen; culture, no growth obtained. Serum